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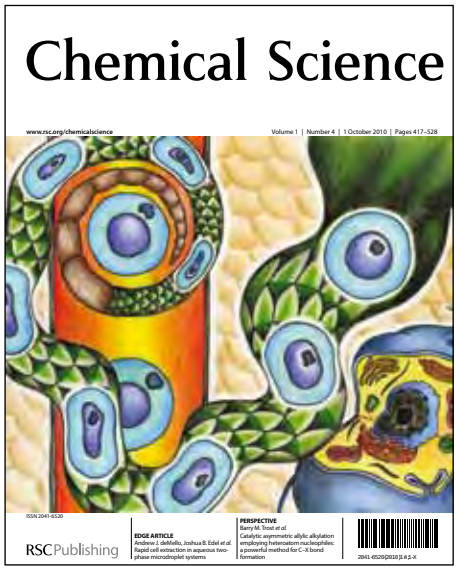

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Edge Article

Copper-Catalyzed Fluorination of 2-Pyridyl Aryl Bromides†

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Copper(I)-catalyzed cross-coupling of aryl halides is the subject of extensive interest in synthetic chemistry, but the related catalytic fluorination is unsuccessful. Herein, we have developed a novel copper-catalyzed fluorination of aryl bromides by using AgF as the fluorine source. In this transformation, pyridyl directing group is essential for the successful catalytic fluorination. XANES/EXAFS study indicated the presence of pyridyl group is essential to stabilize Cu(I) species and accelerate oxidative addition of aryl bromide. Further mechanistic studies implicate a Cu(I/III) catalytic cycle for this Cu(I)-catalyzed fluorination, and final aryl C-F bond formation possibly proceeds through a irreversible reductive elimination of ArCu(III)-F species. This rare observation of catalytic fluorination by copper catalyst provides a valuable foundation for further development of Cu(I)-catalyzed fluorination of aryl halides.

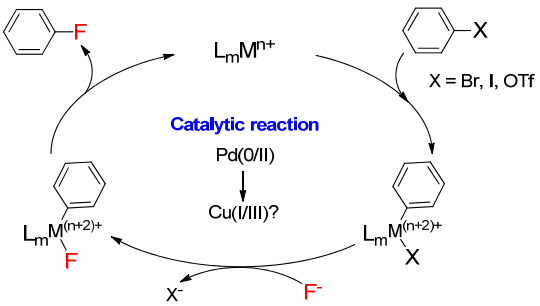
Introduction

Aryl fluorides as essential moieties have received widespread application in pharmaceuticals, agrochemicals and functional materials. Therefore, the development of efficient methodology for aryl C-F bonds formation has attracted much attention.[1] Like in many other areas of catalytic organic transformations, [2] transition metals have been used to catalyze the C-F bond formations.[3] Compared to traditional fluorination reactions, such as Balz-Schiemann reaction and Halex process,[4,5] the catalytic strategy is often highly efficient and encompasses a broad substrate scope.[6]

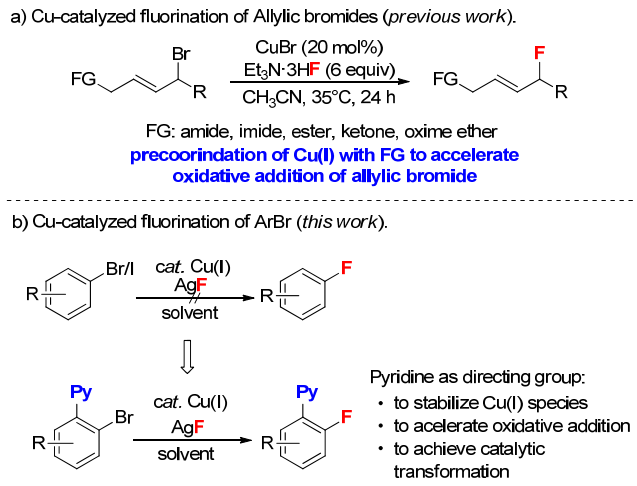
As a class of the cross-coupling reactions,[7] transition metal-catalyzed coupling of aryl halides with inorganic fluorides has attracted much attention for the synthesis of aryl fluorides (Scheme 1). However, this process is highly challenging due to the difficulty in reductive elimination of the ArMF (M = Pd, Rh, etc) species.[8] In 2009, Buchwald and coworkers reported the first example of palladium-catalyzed cross-coupling of aryl triflate with CsF in the presence of (^{t}Bu)Brettphos.[9] Recently, based on the studies of well-defined Cu(III) complexes and related coupling reactions,[10] Ribas[11a] and Wang[11b] reported the pioneer studies on the reductive elimination of macrocyclic ArylCu^{III}F complexes to generate aryl C-F bond. Thus, we envisioned that the inexpensive and abundant copper catalyst might be applied for catalytic fluorination of aryl halides, which would lead to a new catalytic strategy for the late stage synthesis of aryl fluorides.

Early studies on the fluorination of aryl halides provided by Grushin demonstrated that CuF_2 could be used to achieve fluorination of aryl iodides but with very low efficiency.[12] As part of our efforts to develop transition-metal catalyzed fluorinations,[13] we also attempted fluorination of ArBr and ArI using catalytic amount of Cu(I) catalysts. Unfortunately, no desired fluorination product was detected. Quite recently, Hartwig provided a copper-mediate fluorination of aryl iodides using AgF as the fluorine source. [14] However, the reaction required a large excess amount of Cu(I) over AgF, which was tentatively attributed to the competitive oxidation of Cu(I) by AgF to -form the inactive CuF_2. In addition, the method was not suitable for aryl bromides. Our group recently discovered a copper-catalyzed fluorination of allylic bromides. In this transformation, the requirement of a coordinating functional group (FG) on substrate suggests that pre-coordination between FG and Cu(I) catalyst is crucial to the oxidative addition of allylic bromide (Scheme 2a).[15] Based on this finding, we reasoned that introduction of directing group in aryl halides might be helpful to achieve catalytic fluorination. Herein, we reported this study, in which pyridine plays dual roles for the catalytic fluorination. First, *ortho*-pyridyl group is an effective directing group to accelerate oxidative addition step. Second, the presence of pyridine could stabilize Cu(I) species to alleviate its oxidation by AgF. These two important factors thus contribute to the successful catalytic reactions (Scheme 2b).

Scheme 1. Transition Metal-Catalyzed Fluorination of Aryl Halides.



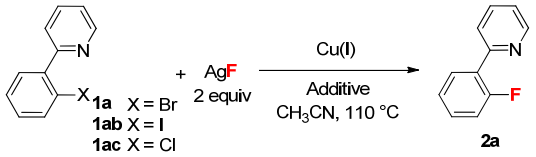
Scheme 2. Cu(I)-catalzyed Fluorination Reactions.



Results and discussion

Initial investigation focused on the screening of a variety of aryl bromides bearing different *ortho*-directing groups under various reaction conditions. When these substrates were treated by $Cu(CH_3CN)_4PF_6$ (1 equiv) and AgF (2 equiv) in CH_3CN, we were delighted to find that pyridine is a good directing group to achieve fluorination reaction. In contrast, other functional groups, such as imine, ester, amide, etc, failed to give the desired products (see the Supporting Information). Further investigation focused on the optimization of reaction conditions. As shown in Table 1, stoichiometric amount of $Cu(CH_3CN)_4PF_6$ was effective to give **2a** in 55% yield (entry 1). However, other copper salts, such as CuBr, CuI, and $[Cu(OTf)]_2{\bullet}C_6H_6$, were ineffective (entries 2-4). Replacement of AgF by combination of silver salts and CsF also provided **2a** in similar yields (entries 5-6). Excitingly, the reaction with catalytic amount of $Cu(CH_3CN)_4PF_6$ also provided **2a** in 38% yield at 120 °C (entry 7). The reaction became sluggish and gave diminished yields when the PF_6 anion was replaced by BF_4 or OTf (entries 8-9). These results indicated the counter ion could influence catalytic efficiency. Thus, exogenous hexafluorophosphate salts were added to adjust the reactivity of copper catalyst. Improved yield was observed in the presence of Bu_4NPF_6 (entry 12). However, KPF_6 and Me_4NPF_6 gave inferior results (entries 10-11). Concentrated reaction provided better yield (entry 13). Compared to stoichiometric reaction, replacement of AgF by AgOTf/CsF gave very low yield in catalytic reaction (entries 5 vs 14). Addition of nitrogen- or oxygen-containing ligands were not helpful to improve reaction yields (see Supporting Information). Contrary to inactive CuBr, surprisingly, copper complex **A** gave similar results with $Cu(CH_3CN)_4PF_6$, but copper complexes **B** and **C** gave slightly lower yields (entry 15-17 & Figure 1). No reaction occurred in the absence of copper catalyst. Finally, other 2-pyridyl-phenylhalide reactions were investigated. The reaction of 2-pyridyl-phenyl iodide **1ab** exhibited a similar reactivity with **1a**, but 2-pyridyl-phenyl chloride **1bc** was inactive toward fluorination (entries 18-19).

Table 1. Screening Results.[a]



Entry	Substrate	[Cu] (mol%)	Additive	Yield(%)[b]
1	**1a**	$[Cu(MeCN)_4]PF_6$ (100)	--	55
2	**1a**	CuBr (100)	--	0
3	**1a**	CuI (100)	--	0
4	**1a**	$[Cu(OTf)]_2{\cdot}C_6H_6$ (100)	--	0
5[c]	**1a**	$[Cu(MeCN)_4]PF_6$ (100)	--	44
6[d]	**1a**	$[Cu(MeCN)_4]PF_6$ (100)	--	57
7[e]	**1a**	$[Cu(MeCN)_4]PF_6$ (20)	--	38
8[e]	**1a**	$[Cu(MeCN)_4]OTf$ (20)	--	31
9[e]	**1a**	$[Cu(MeCN)_4]BF_4$ (20)	--	29
10[e]	**1a**	$[Cu(MeCN)_4]PF_6$ (20)	KPF_6 (1 equiv)	10
11[e]	**1a**	$[Cu(MeCN)_4]PF_6$ (20)	Me_4NPF_6 (1 equiv)	38
12[e]	**1a**	$[Cu(MeCN)_4]PF_6$ (20)	*n*-Bu_4NPF_6 (1 equiv)	53
13[e,f]	**1a**	$[Cu(MeCN)_4]PF_6$ (20)	*n*-Bu_4NPF_6 (1 equiv)	**65**
14[c]	**1a**	$[Cu(MeCN)_4]PF_6$ (20)	*n*-Bu_4NPF_6 (1 equiv)	16
15[e,f]	**1a**	Cu complex **A** (20)	--	**63**
16[e,f]	**1a**	Cu complex **B** (20)	--	42
17[e,f]	**1a**	Cu complex **C** (20)	--	39
18[e,f]	**1ab**	$[Cu(MeCN)_4]PF_6$ (20)	*n*-Bu_4NPF_6 (1 equiv)	62
19[e,f]	**1ac**	$[Cu(MeCN)_4]PF_6$ (20)	*n*-Bu_4NPF_6 (1 equiv)	trace

[a] Reaction condition: **1** (0.1 mmol) in 1.0 mL of CH_3CN. [b] Yield determined by ^{19}F-NMR spectroscopy with benzotrifluoride as the internal standard. [c] AgF was replaced by AgOTf/CsF (2 equiv). [d] AgF was replaced by $AgBF_4$/CsF (2 equiv). [e] Reaction was carried out at 120 °C. [f] The concentration was 0.2 M.

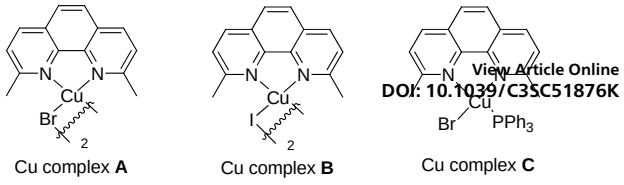
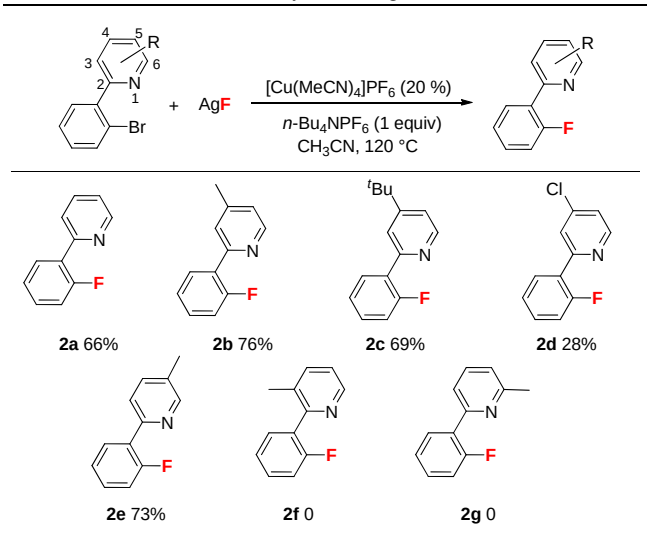


Figure 1. The Structure of Copper Complexes.

Table 2. Substutient Effects on Pyridine Ring.[a]

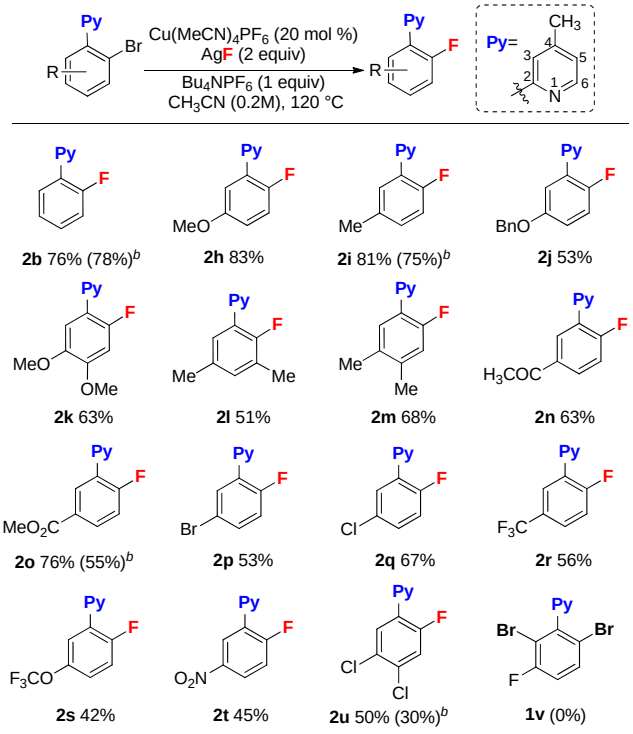


[a] Rections were run at 0.2 mmol scale, isolated yield.

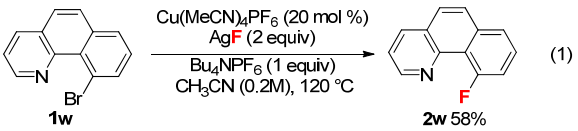
Next, we explored the substituent effects on pyridyl ring (table 2). The electron-donating group provided much superior results than weak electron-withdrawing group. For instance, substrates **1b** (4-Me) and **1c** (4-*t*- Bu) gave better results than that of **1a**, but substrate **1d** (4-Cl) provided lower yield. These results suggested that electron-donating pyridyl group significantly improved the fluorination process. In addition, the positions of methyl group also influenced fluorination. Methyl group located at 4° (**1b**) and 5° (**1e**) position provided similar results, but at 3° (**1f**) and 6° (**1g**) could not deliver the corresponding fluorination products.

With optimized reaction conditions in hand, substrate scope with a variety of substituents on benzene ring were then investigated (Table 3). Compared to Halex process which is only suitable for electron-poor aryl compounds, electron-rich aryl bromides were compatible with this reaction condition. For instance, aryl bromides bearing one or two electron-donating groups gave moderate to good yields (**2b, 2h-2m**). Electron-poor substrates were also suitable for reaction condition to give satisfactory yields. In those reactions, various functional groups, such as ketone (**2n**), ester (**2o**), halogen (**2p-2q**) and trifluoromethyl (**2r**), survived in this transformation. Substrates bearing trifluoromethoxyl and nitro groups delivered the corresponding products (**2s-2t**) in slightly low yields (42% and 45%). It is worth noting that, for substrate **1p** containing two bromides, only *ortho*-position bromides was reactive. For more electron-poor substrate **1u** with two chlorides and one bromide, the reaction also proceeded smoothly to afford fluorination product **2u** in 50% yield without replacement of chlorine by fluorine. Those observations again addressed the vital role of pyridyl group to promote the fluorination. Unfortunately, substrate **1v** bearing two *ortho*-bromides failed to give fluorination product. For electron-rich aryl bromides (such as **1b**, **1i**), it should be pointed out that Cu complex **A** presented a similar reactivity with cationic copper catalyst to give compatible yields, but with slightly lower reactivity for electron-poor substrates (**1o**, **1u**). Finally, Bromobenzo-[h]quinoline **1w** was a good substrate to give product **2w** in 58% yield (eq 1).

Table 3. Substrate Scope of Fluorination of Aryl Bromides.[a]



[a] Reactions were run at 0.2 mmol scale, isolated yield. [b] The data in parenthesis was obtained under condition with copper complex **A** (entry 15 in table 1).



Mechanism

Compared to substrate **1**, standard condition was not suitable for the fluorination of simple iodobenzene due to the lack of pyridyl group. It is possible that the coordination of pyridyl with Cu(I) may be helpful to stabilize Cu(I) species in the excess amount of AgF and achieve the catalytic fluorination. In order to test this hypothesis, XANES/EXAFS analysis of reaction residues of PhI and **1b** provided further insight inthis scenario. For the case of PhI, Cu(I) reagent was fully oxidized to Cu(II) species, in which the peak on 8982 KeV was absent and new signal at 8978 KeV appeared.[16] In contrast, Cu(I) species still existed in the case of **1b**, in which oxidation of Cu(I) was suppressed (Figure 2).[17] These results revealed that the coordination of pyridyl group is vital for stabilization of Cu(I) species.

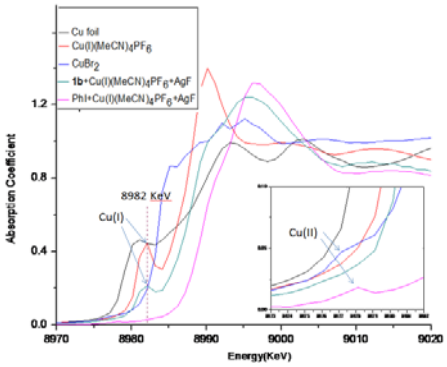
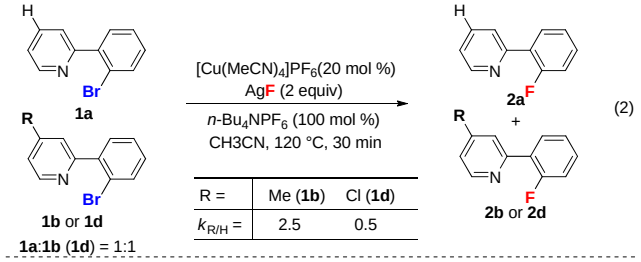


Figure 2. XANES/EXAFS analysis on Cu species.

In addition, as shown in eq 2, substrates **1b** bearing electron-donating group on pyridine ring reacted significantly faster than substrate with electron-withdrawing group (**1d**). The possible reason is that the electron-rich pyridyl group could enhance nucleophilicity of Cu(I) to facilitate oxidative addition towards aryl C-Br bond.

To probe the electronic effect of aryl bromides, a series of competing reactions were carried out. A mixture of substrates **1b** (R= H) and **1i** (**1r** or **1o**) with 1:1 ratio was subjected to the standard reaction condition for 20 min to allow low conversion (less than 20%). As shown in eq 3, electron-rich substrate (**1i**) exhibited faster rate than electron-poor substrate (**1r** or **1o**). This phenomenon is consistent with a Cu(I)/Cu(III) catalytic cycle, which was reported in the copper-catalyzed C-C bond formation

reaction.[18] Recently, Fu and Peters reported a Cu-catalyzed Ullman C-N coupling involving a single electron transfer (SET) mechanism, in which electron-deficient aryl halides react faster than electron-donating substrates.[19] The observed opposite reactivity indicates that the SET pathway is less likely in the present cases.



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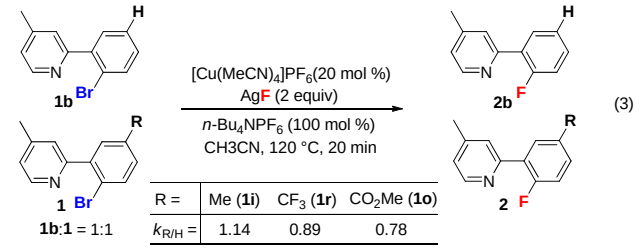
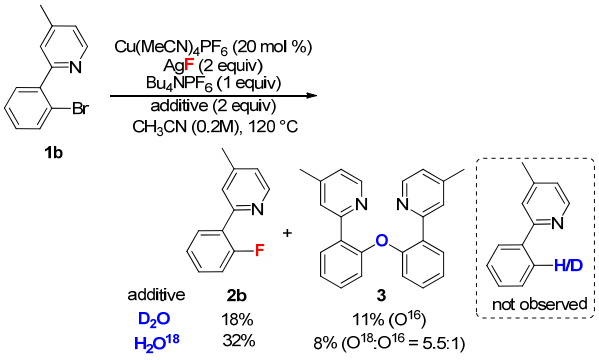


(3)

During the optimization of reaction conditions, trace amount of side product **3** (less than 5%) was detected. In contrast, the corresponding dehalogenation product was not observed.[20] In order to address the formation of **3**, the reaction of **1b** was conducted in the presence of D_2O or H_2O^{18}. As shown in eq 4, the yield of **2b** was obviously decreased in the presence of water, and **3** was isolated in low yield. In the case of H_2O^{18}, the incorporation of O^{18} revealed that product **3** should be derived from the reaction of **1b** with water.[21] When MeOH was used as additive, the reaction afforded major methoxylation product **4** in 54% yield, along with 34% of the fluorination product **2b**. When MeOH was used as co-solvent, the reaction afforded product **4** in 80% yield, but with trace amount of **2b** (eq 5). Hartwig and coworkers recently reported a copper-mediated fluorination of iodobenzene.[14] In this reaction, significant amount of dehalogenation side product was observed, which was attributed to the radical pathway.[19,22] In contrast, the related dehalogenation reaction did not occur in current transformation, even in the presence water (eq 4). Combined with the formation of **3** and **4** and other experimental observations we suggest that current reaction possibly involves a Cu(I/III) pathway.[10]



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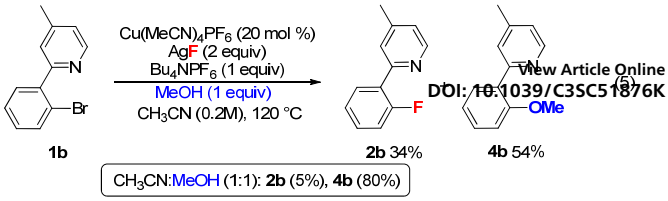

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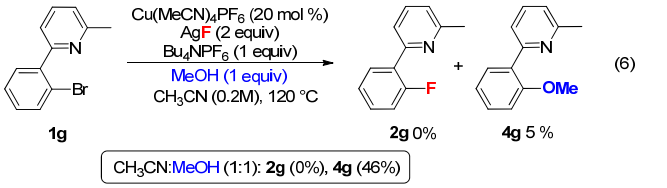
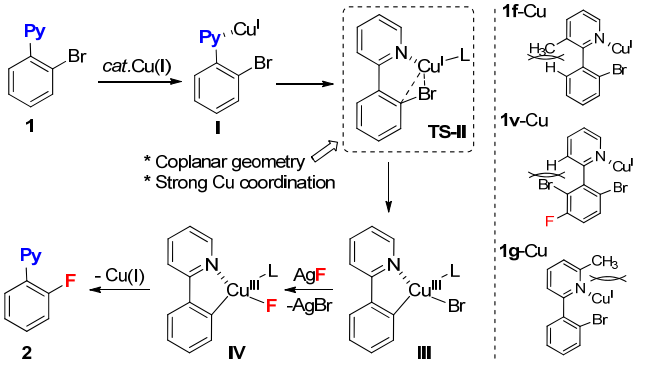


(6)

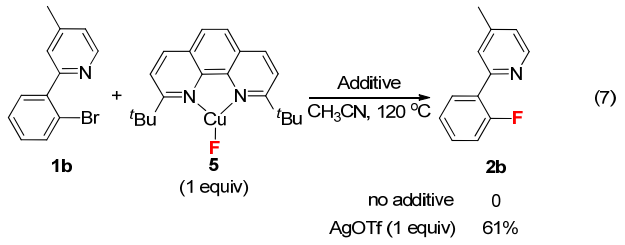
As mentioned in Table 2, substrate **1g** was inert for the fluorination due to the steric effect. In contrast, the reaction of **1g** delivered product **4g** in 46% yield in large excess amount of MeOH, but provided trace amount of **4g** in stoichiometric amount of MeOH (eq 6).[23] Those observations revealed that methoxylation of aryl bromide **1g** also exhibited similar steric effect. However, compared to above methoxylation, no fluorination reactivity of **1g** (in Table 2) implied that the oxidative addition of aryl C-Br bond by $PyCu^{I}L$ (Py = **1g**, L = F or CH_3CN) is slower than that of $PyCu^{I}(OMe)$.[24]

Based on above results, the mechanism is proposed as shown in Scheme 3. The initial pre-coordination of substrate **1** with Cu(I) promote an intramolecular oxidative addition to give the Cu(III) intermediate **III**. Subsequent ligand exchange with AgF and irreversible reductive elimination of **IV** provided the fluorination product **2**.[25] In this catalytic cycle, two additional requirements should be mentioned: (1) a coplanar geometry of complex **I** is required for this reaction. Substrate **1f**, which lacks the coplanar geometry due to the repulsion between 3-methyl and *ortho*-H (**1f**-Cu), could not deliver the fluorinated product. Similar effect was observed for substrate **1v**. (2) The unsuccessful fluorination of substrate **1g** with 6-methyl group is possibly attributed to the weakened coordination due to steric effect, which also indicated that strong coordination ability of substrate is crucial for the reaction. Above unfavorable steric effects might destabilize the transition state (TS-**II**) or the Cu(III) ground state **III**.

Scheme 3. Proposed Mechanism.



Finally, the screening of the common fluorine source demonstrated that only AgF could deliver the product. Other inorganic fluorides were ineffective to yield fluorinationproduct (see Supporting Information). Although these results indicated that AgF plays an important role in this transformation, the detailed mechanism is still unknown at the moment. A possible explanation is that the presence of silver salt is helpful to activate C-Br bond and trap bromide ion in aryl-Cu(III) complex **III** to generate complex **IV**, which resulted the C-F bond formation. For the case of other inorganic fluorides, removal of bromide ion became more difficult. Thus, instead of complex **IV** formation, the reaction of complex **III** could go back to aryl bromide via reductive eliminations , or generate other side product. In order to provide further insight on this point, the isolated CuF complex **5**[26] was applied to stoichiometric reaction. Interestingly, no fluorination occurred, but product **2b** was obtained in the presence of AgOTf (eq 7). These results are consistent with above analysis



(7)

Conclusions

We have developed a novel copper-catalyzed fluorination of aryl bromides with AgF, in which pyridyl groups are important for this catalytic fluorination. Preliminary mechanistic studies indicated the coordination of pyridyl group with Cu(I) could stabilize Cu(I) species and accelerate oxidative addition of aryl bromide. Final aryl C-F bond formation possibly undergoes a irreversible reductive elimination of ArCu(III)-F species. Due to current substrate limitation bearing pyridyl directing group, further expansion of substrate scope and application of this chemistry is in progress.

Acknowledgments

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Notes and references

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† Electronic Supplementary Information (ESI) available: Full experimental procedure and spectroscopic characterization data are provided. See DOI: 10.1039/b000000x/

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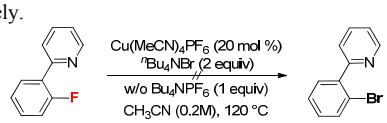
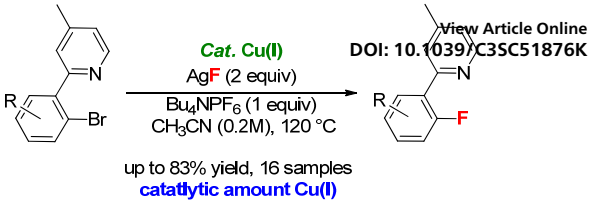


2a 1a

26 Y. Liu, C. Chen, H. Li, J. Tan, K.-W. Huang, Y. Yuan, Z. Weng, 2013, *Manuscript submitted to Journal.*



Graphic Abstract: